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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	AVRAMOFF et al	GROUP ART UNIT.:	1618
SERIAL NUMBER:	10/575,809	CONFIRMATION NO:	5244
FILING DATE:	13 April 2006	EXAMINER:	WESTEBERG, Nissa M

TITLE: STABLE LANSOPRAZOLE FORMULATION

Commissioner for Patents
P.O. Box 1450
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REVISED APPEAL BRIEF

Sir:

Applicant has appealed to the Board of Patent Appeals and Interferences from the non-final decision of the Examiner issued on November 23, 2009, rejecting claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59. This is a further revised version, submitted in response to the Notice sent on August 23 2010, which is being timely filed by September 23 2010. The complete Appeal is being submitted with the separate revised claims as a separate document as well. In response to the Notice of Panel Decision from Pre-Appeal Brief Review issued March 19, 2010, Applicant respectfully submits herewith the revised appeal brief.

REAL PARTY IN INTEREST

The present application is owned by Dexcel Ltd, which is the real party in interest.

RELATED APPEALS AND INTERFERENCES

There are no known appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this pending appeal.

STATUS OF CLAIMS

Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 stand rejected pursuant to a Non-Final Rejection issued November 23, 2009. Claims 39 and 40 were also objected to in this Non-Final Rejection. Claims 1-6, 8, 10-16, 18, 20, 21, 23-25, 51-57 have been withdrawn. Claims 7, 9, 17, 19, 22, 33, 35, 43, 45 and 48 have been canceled. Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 are presented for appeal.

STATUS OF AMENDMENTS

No amendment was filed after a Non Final Rejection of 23 November 2009.

SUMMARY OF CLAIMED SUBJECT MATTER

With respect to independent claim 26, there is provided a method of administering a therapeutically effective amount of lansoprazole as sole pharmaceutically active ingredient. The method comprises orally administering a stable composition for lansoprazole (see Example 7 on page 16, lines 6-15), the composition comprising a substrate, a subcoating layer for coating the substrate, and an enteric layer over the subcoating layer. The substrate comprises lansoprazole or a pharmaceutically suitable salt thereof. The substrate does not include an alkaline agent (see page 3, lines 5-9). The subcoating layer consists essentially of sodium stearate, a cellulosic polymer selected from hydroxypropyl methylcellulose, ethylcellulose and hydroxypropyl cellulose, or a mixture thereof; a filler; a surfactant selected from polysorbate 80 and sodium lauryl sulfate; and a solvent (see page 4, lines 14-30).

With respect to independent claim 27, there is provided a method of administering a therapeutically effective amount of lansoprazole. The method comprises orally administering a stable composition for lansoprazole (Example 7, page 16, lines 6-15), the composition comprising a substrate, a

subcoating layer for coating the substrate, and an enteric layer over the subcoating layer (page 3, lines 5-9). The substrate comprises lansoprazole or a pharmaceutically suitable salt thereof as a sole pharmaceutically active ingredient (see Example 1 on page 10). The substrate does not include an alkaline agent (see page 3, lines 5-9). The subcoating layer comprises sodium stearate as alkaline agent (see page 4, lines 14-15).

With respect to independent claim 58, there is provided a method of administering a therapeutically effective amount of lansoprazole. The method comprises orally administering a stable composition for lansoprazole (Example 7 on page 16, lines 6-15), the composition comprising a substrate, a subcoating layer for coating the substrate, and an enteric layer over the subcoating layer (see page 3, lines 5-9). The substrate comprises an active core containing lansoprazole or a pharmaceutically suitable salt thereof as sole pharmaceutically active ingredient, and a surfactant (Example 1 on page 10, lines 1-29, bridging to page 11, lines 1-19 and to page 12, lines 1-8 and page 4, lines 7-10). The substrate does not include an alkaline agent (page 3, lines 3-9). The subcoating layer comprises sodium stearate as alkaline agent (page 4, lines 14-15).

With respect to independent claim 59, there is provided a method of administering a therapeutically effective amount of lansoprazole. The method comprises orally administering a stable composition for lansoprazole (Example 7 on page 16, lines 6-15), the composition comprising a substrate, a subcoating layer for coating the substrate, and an enteric layer over the subcoating layer (page 3, lines 5-9). The substrate comprises a neutral core and an active coating layered over the neutral core (page 3, lines 22-24). The active coating contains lansoprazole or a pharmaceutically suitable salt thereof as sole pharmaceutically active ingredient, and a surfactant (Example 1 on page 10, lines 1-29, bridging to page 11, lines 1-19 and to page 12, lines 1-8, and page 4, lines 7-10). The substrate does not include an alkaline agent (page 3, lines 3-9). The subcoating layer comprises sodium stearate as alkaline agent (page 4, lines 14-15).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 26-32, 34, 36-40, 42, 44, 46, 47, 49, 50, 58 and 59 are rejected as being obvious under 35 U.S.C. 103(a) over WO 96/24375 to Depui in view of EP1174136 to Lundberg and U.S. 6,210,712 to Edgren et al.

2. Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 are rejected as obvious under 35 U.S.C. 103(a) over WO 96/24375 to Depui in view of EP1174136 to Ludberg and U.S. 6,210,712 to Edgren et al., and further in view of US 2002/0150618 to Napper et al.

3. Claims 26-32, 34, 36, 38-42, 44, 46, 47, 49, 50, 58 and 59 are rejected as obvious under 35 U.S.C. 103(a) over US 2002/0155153 to Depui in view of EP1174136 to Lundberg and U.S. 6,210,712 to Edgren et al.

4. Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 are rejected as obvious under 35 U.S.C. 103(a) over US 2002/0155153 to Depui, EP1174136 to Lundberg and U.S. 6,210,712 to Edgren et al. further in view of WO 96/24375 to Depui and US 2002/0150618 to Napper et al.

5. The Examiner has further objected to claims 39 and 40 under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

6. The Examiner has rejected claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 under USC 112, first paragraph as failing to comply with the written description requirement by introducing new matter in the form of the limitation that lansoprazole is "sole pharmaceutically active ingredient".

ARGUMENTS

1. Claims 26-32, 34, 36-40, 42, 44, 46, 47, 49, 50, 58 and 59 stand rejected for the above grounds and are hereby argued as a group.

In the Office Action of March 12, 2009, the Examiner argues that WO '375 discloses an oral, enteric coated dosage form comprising an acid labile proton pump inhibitor useful in the treatment of disorders associated with *Heliobacter* infections, and preparation of a multilayer dosage form comprising lansoprazole in free base form. The core of the WO '375 dosage form contains a sugar sphere seed (neutral core) coated with lansoprazole, the cellulosic polymer HPMC and water as aqueous solvent. No alkaline material is present in the core. The separating layer comprises the cellulosic polymer HPC, the filler talc, magnesium stearate and the solvent water. An enteric coating layer comprising a methacrylic acid copolymer and the plasticizer triethyl citrate is present in the dosage form. The active ingredient can be mixed with other ingredients such as binders, surfactants and fillers.

The Examiner stated that Depui '375 teaches a formulation which differs from that of the present invention in that a surfactant and filler are present in the same layer as the active ingredient, and which does not disclose the use of sodium stearate in the subcoating layer. The Examiner

states that Lundberg discloses use of a surfactant and magnesium stearate in the subcoating layer of a formulation comprising a proton pump inhibitor

The Examiner also referred to Edgren, which, according to the Examiner, discloses that potassium stearate, magnesium stearate and sodium stearate are functionally equivalent.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to prepare a multi-layer dosage form as disclosed by WO '375 and to use sodium stearate and a surfactant such as polysorbate 80 or sodium lauryl sulfate in the subcoating layer. According to the Examiner, the person of ordinary skill in the art would have been motivated to use sodium stearate, and reasonably would have expected success because WO '375 and Ludgren teach that magnesium stearate can be used in the subcoating layer, and Edgren et al. discloses that magnesium stearate and sodium stearate are functionally equivalent, as they are both lubricants. The rejections were maintained in the Office Action of November 23, 2009.

The Examiner's rejections are traversed for the following reasons. The characterizing feature of the formulation of the present invention is that the substrate is devoid of an alkaline agent, while an alkaline agent is provided in the separating layer. This feature is recited in the claims and is

described as detailed in the above Claim Summary. The above references, alone or in combination, do not teach this feature.

The Examiner referred to specific examples of Depui '375 which included magnesium stearate in the subcoating layer, and which the Examiner referred to as an alkaline agent. However, magnesium stearate is referred to in the '375 specification as an example of an additive such as a plasticizer, colorant, pigment, filler, anti-tacking agent or antistatic agent, and is not included in the list of possible alkaline agents given elsewhere in the specification (page 15 throughout). Furthermore, the amount of magnesium stearate is clearly not sufficient to act as anything other than a lubricant; for example, in Example 1 (page 22), the amount of magnesium stearate is less than 2%. In such low quantities, it could not act as an alkalizing agent.

Magnesium stearate is insoluble in ethanol, ether and water, hence cannot be defined as an alkaline agent, in contrast to sodium stearate which is the alkalinizing agent of the instant application, such that the two cannot be considered functionally equivalent as alkalinizing agents. The magnesium stearate in the subcoating layer of the cited art will not change the pH of that layer.

Moreover, the functional equivalence of magnesium stearate and sodium stearate described by Edgren et al. was taught in the context of use as lubricating agents and not as alkalinizing agents (col 6, lines 35-45). No evidence is offered by the Examiner that magnesium stearate and sodium stearate are functionally equivalent as alkalinizing agents.

It would not be obvious in view of the teachings of the equivalence of the stearates as lubricating agents to use sodium stearate instead of magnesium stearate as alkalinizing agent, which is an entirely different purpose. Applicant has previously submitted evidence in the form of pages from the US Pharmacopeia (provided in the amendment of September 12 2009) showing the differences in solubility between the two stearates, which determine their ability to function as alkalinizing agents. In view of the low solubility of magnesium stearate in water and various organic solvents, this compound cannot be considered to function as an alkalinizing agent, in complete contrast to sodium stearate. Hence, the use of sodium stearate as an alkalinizing agent cannot be considered obvious in view of the use of an entirely different stearate, i.e. magnesium stearate, for an entirely different function, i.e. that of a lubricant.

Furthermore, an alkali is defined as 'any of various water-soluble compounds capable of turning litmus blue and reacting with an acid to form a salt and water', a printed copy of which is attached herewith. Thus, clearly magnesium stearate cannot be effective as an alkalizing agent; furthermore, none of the references cited by the Examiner or available to Applicant suggest that in fact magnesium stearate could be effective as an alkalizing agent.

In the Office Action dated November 23, 2009, the Examiner maintained that since magnesium stearate and sodium stearate are disclosed as being functionally equivalent as lubricants, they are also functionally equivalent for the role of alkalinizing agents. The Examiner states as follows: ' *Because sodium stearate and magnesium stearate are slightly different compounds, one of ordinary skill in the art would not expect these two compounds to have exactly the same properties. Applicants arguments about the different properties of the two stearate compounds would be germane if the stated purpose of the stearate ingredient in the cited prior art was to function as an alkaline agent, but that is not the stated purpose of the cited prior art'.*

Applicant finds this argument confusing, as the Examiner is maintaining that these very different stearate compounds, which are taken as being functionally equivalent for one purpose may also be considered equivalent for an entirely different purpose, even though the Examiner acknowledges that the compounds would not be expected to have exactly the same properties.

Depui '375 does not disclose magnesium stearate as being suitable for use as an alkaline agent in the separating layer, hence following the teaching of Depui '375 in combination with Ludberg and Edgren would not result in the formulation of the present invention.

Additionally, Depui '375 referred to by the Examiner comprises omeprazole and not lansoprazole as active ingredient, as stated throughout the reference, which are not interchangeable.

Furthermore, the active ingredient of the present invention is preferably the base of lansoprazole, whereas Depui '375 discloses the magnesium salt of omeprazole, which is significantly more stable than the base form, and thus does not require an alkalizing agent for stabilization.

Hence, for the reasons detailed above, Applicant considers claims 26-32, 34, 36-40, 42, 44, 46, 47, 49, 50, 58 and 59 to be novel and non-obvious over Depui '375, Lundberg and Edgren, alone or in combination.

2. Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 stand as being rejected for the above grounds and are hereby argued as a group.

As discussed above, Applicant considers all claims of the instant application to be patently distinct from the Depui WO '375, Lundberg, Edgren et al. combination.

Since, as detailed above, combination of the teachings of Depui WO '375, Lundberg and Edgren et al does not result in the formulation of the present invention, which is characterized in that the substrate is devoid of an alkaline agent, while an alkaline agent is provided in the separating layer, the use of lactose monohydrate in such a formulation would similarly not result in the formulation of the present invention.

Hence, Applicant considers claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 to be novel and non-obvious over Depui '375, Lundberg, Edgren et al and Napper, alone or in combination.

3. Claims 26-32, 34, 36, 38-42, 44, 46, 47, 49, 50, 58 and 59 stand rejected for the above grounds and are hereby argued as a group.

As stated by the Examiner, Depui '153 does not explicitly disclose a lansoprazole preparation in which an inorganic or organic basic salt is present in the separating layer, or the inclusion of sodium stearate, polysorbate 80 and/or sodium lauryl sulfate in the subcoating layer.

Lundberg et al discloses a trilayer (active ingredient core, intermediate layer and enteric layer) dosage form containing proton pump inhibitor compounds, according to the Examiner. The Examiner argues that Example 1 teaches a dosage form comprising a separating layer, which includes magnesium stearate as alkaline agent. The Examiner further argues that Edgren et al disclose that potassium stearate, magnesium stearate and sodium stearate are functionally equivalent.

As discussed in detail above, Applicant respectfully argues that magnesium stearate is not an alkalinizing agent. The functional equivalence of magnesium stearate and sodium stearate described by Edgren et al. was taught in the context of use as lubricating agents and not as alkalinizing agents (citation above). No evidence is offered by the Examiner that magnesium stearate and sodium stearate are functionally equivalent as alkalinizing agents. By contrast and as previously described, Applicant has actually provided evidence that these two agents instead were not

functionally equivalent as alkalinizing agents, through a previously provided copy of the relevant entries from the USP (provided in the amendment of September 12 2009), which demonstrated that magnesium stearate is not soluble in water while sodium stearate is soluble in water.

Since, as detailed above, the combination of the teachings of Depui '153, Lundberg and Edgren et al does not result in the formulation of the present invention, which is characterized in that the substrate is devoid of an alkaline agent, while an alkaline agent is provided in the separating layer.

Hence, Applicant considers claims 26-32, 34, 36, 38-42, 44, 46, 47, 49, 50, 58 and 59 to be novel and non-obvious over Depui '153, Lundberg, and Edgren et al, alone or in combination.

4. Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 stand rejected for the above grounds and are hereby argued as a group.

As discussed in detail above, the subcoating layer of Depui is not taught as containing sodium stearate, but rather magnesium stearate, which is not functionally equivalent as an alkalinizing agent. Hence, the combination of Depui '153, Lundberg and Napper et al does not result in the formulation of the present invention, which is characterized in that the substrate is devoid of an alkaline agent, while an alkaline agent is provided

in the separating layer. Further combination of the cited documents with Depui '375 and/or Napper to provide a dosage form comprising lactose as filler in the layer with the lansoprazole would therefore not result in the formulation of the present invention.

Hence, Applicant considers claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 to be novel and non-obvious over Depui '153, Lundberg, Edgren, Depui '375, and Napper, alone or in combination.

5. Claim 39 is objected to by the Examiner for the above grounds and is hereby argued separately. Applicant does not agree as claim 39 refers to an organic basic salt as an additional agent.

Claim 40 is objected to by the Examiner for the above grounds and is hereby argued separately. Applicant acknowledges that claim 40 does fail to further limit the subject matter of the previous independent claim 27.

6. Claims 26-32, 34, 36-42, 44, 46, 47, 49, 50, 58 and 59 have been rejected for the above grounds and are hereby argued as a group. Applicant respectfully traverses this rejection. First, all formulations disclosed in the present application relate to lansoprazole. Second, as described for example in page 1 lines 3-7, page 3 lines 5-8, page 5 lines 16-21 of the application, and indeed throughout the application, the formulation

is described throughout as being a "formulation for lansoprazole". The original claims as filed also recite "a formulation for lansoprazole". Example 7 on page 16, lines 6-15, relates to methods of administration of lansoprazole only. In MPEP 608.01(o), it is stated "an applicant is not limited to the nomenclature used in the application as filed". MPEP 2163.05 states "each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure". Applicant respectfully argues that the limitation of "sole pharmaceutically active ingredient" in relation to lansoprazole is both implicitly and inherently support in the present application for the reasons given above.

CONCLUSION

Applicant has clearly demonstrated that the present invention as claimed is clearly distinguishable over all the art cited of record, either alone or in combination, and satisfies all requirements under 35 U.S.C 103. Therefore, Applicant respectfully requests the Board of Patent Appeals and Interferences to reverse the rejection of the Examiner and instruct the Examiner to issue a notice of allowance of all claims.

Respectfully submitted,

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APPENDIX OF CLAIMS

1. (Withdrawn) A stable composition for lansoprazole, the composition comprising:

(a) a substrate, said substrate comprising lansoprazole or a pharmaceutically suitable salt thereof;

(b) a subcoating layer comprising an alkaline agent; and

(c) an enteric coating material layered over said subcoating layer; wherein said substrate is characterized in that said substrate does not include an alkaline agent.

2. (Withdrawn) The composition of claim 1, wherein lansoprazole comprises lansoprazole base.

3. (Withdrawn) The composition of claim 1, wherein said substrate features:

(i) a neutral core; and

(ii) an active coating containing lansoprazole, said active coating being layered over said neutral core;

such that the composition is in a form of a pellet.

4. (Withdrawn) The composition of claim 3, wherein said neutral core comprises a non pareil.

5. (Withdrawn) The composition of claim 4, wherein said non-pareil has a range in a size of from about 300 to about 1000 microns.

6. (Withdrawn) The composition of claim 3, wherein said active coating includes at least one cellulosic polymer selected from the group consisting of hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC), or a mixture thereof.

7. (Canceled)

8. (Withdrawn) The composition of claim 3, wherein said active coating comprises at least one surfactant selected from the group consisting of of Tween 80 or sodium lauryl sulfate.

9. (Canceled)

10. (Withdrawn) The composition of claim 3, wherein said active coating further comprises at least one filler.

11. (Withdrawn) The composition of claim 10, wherein said at least one filler comprises a suitable grade of lactose.

12. (Withdrawn) The composition of claim 3, wherein said active coating further comprises an aqueous solvent.

13. (Withdrawn) The composition of claim 1, wherein said alkaline agent in said subcoating layer comprises an organic basic salt.

14. (Withdrawn) The composition of claim 13, wherein said organic basic salt includes at least one of sodium stearate.

15. (Withdrawn) The composition of claim 1, wherein said alkaline agent in said subcoating layer comprises an inorganic basic salt.

16. (Withdrawn) The composition of claim 1, wherein said subcoating layer includes at least one cellulosic polymer selected from the group consisting of hydroxypropyl methylcellulose (HPMC), ethylcellulose and hydroxypropyl cellulose (HPC), or a mixture thereof.

17. (Canceled)

18. (Withdrawn) The composition of claim 1, wherein said subcoating layer comprises at least one surfactant selected from the group consisting of Tween 80 or sodium lauryl sulfate.

19. (Canceled)

20. (Withdrawn) The composition of claim 1, wherein said enteric coating material includes at least one enteric material selected from the group consisting of hydroxypropyl methylcellulose acetate succinate,

polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylic acid methyl methacrylate and polymethacrylic acid ethyl methacrylate.

21. (Withdrawn) The composition of claim 1, wherein said enteric coating material further comprises a plasticizer selected from the group consisting of a citric acid ester and a phthalic acid ester.

22. (Canceled)

23. (Withdrawn) The composition of claim 1, wherein said substrate is an active core for containing lansoprazole.

24. (Withdrawn) The composition of claim 23, wherein said active core is selected from the group consisting of a pellet, a bead and a tablet.

25. (Withdrawn) A stable composition for lansoprazole, the composition comprising:

(a) a substrate, said substrate comprising lansoprazole or a pharmaceutically suitable salt thereof;

(b) a subcoating layer for coating said substrate, said subcoating layer consisting essentially of an alkaline agent, a cellulosic polymer, a filler, a surfactant and a solvent; and

(c) an enteric coating material layered over said subcoating layer.

26. (Previously presented) A method for administering a therapeutically effective amount of lansoprazole as sole pharmaceutically active ingredient to a subject comprising:

administering orally to the subject a stable composition for lansoprazole comprising:

(a) a substrate, said substrate comprising lansoprazole or a pharmaceutically suitable salt thereof, wherein said substrate is characterized in that said substrate does not include an alkaline agent,

(b) a subcoating layer for coating said substrate, said subcoating layer consisting essentially sodium stearate, a cellulosic polymer selected from the group consisting of hydroxypropyl methylcellulose (HPMC), ethylcellulose and hydroxypropyl cellulose (HPC), or a mixture thereof, a filler, a

surfactant selected from the group consisting of polysorbate 80 and sodium lauryl sulfate, and a solvent; and

(c) an enteric coating material layered over said subcoating layer.

27. (Previously presented) A method for administering a therapeutically effective amount of lansoprazole to a subject comprising:

administering orally to the subject a stable composition for lansoprazole comprising:

(a) a substrate, said substrate comprising lansoprazole or a pharmaceutically suitable salt thereof as sole pharmaceutically active ingredient, wherein said substrate is characterized in that said substrate does not include an alkaline agent;

(b) a subcoating layer for coating said substrate, said subcoating layer comprising an alkaline agent comprising sodium stearate; and

(c) an enteric coating material layered over said subcoating layer.

28. (Original) The method of claim 27, wherein lansoprazole comprises lansoprazole base.

29. (Previously presented) The method of claim 27, wherein said substrate features:

(i) a neutral core; and

(ii) an active coating containing lansoprazole, said active coating being layered over said neutral core;

such that the composition is in a form of a pellet.

30. (Original) The method of claim 29, wherein said neutral core comprises a non pareil.

31. (Original) The method of claim 30, wherein said non-pareil has a range in a size of from about 300 to about 1000 microns.

32. (Previously presented) The method of claim 29, wherein said active coating includes at least one cellulosic polymer selected from the group consisting of hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC), or a mixture thereof.

33. (Canceled)

34. (Previously presented) The method of claim 29, wherein said active coating comprises at least one surfactant selected from the group consisting of polysorbate 80 and sodium laurel sulfate.

35. (Canceled)

36. (Previously presented) The method of claim 29, wherein said active coating further comprises at least one filler.

37. (Previously presented) The method of claim 36, wherein said at least one filler comprises lactose monohydrate.

38. (Previously presented) The method of claim 29, wherein said active coating further comprises an aqueous solvent.

39. (Previously presented) The method of claim 27, wherein said alkaline agent in said subcoating layer comprises an organic basic salt.

40. (Previously presented) The method of claim 39, wherein said organic basic salt comprises sodium stearate.

41. (Previously presented) The method of claim 27, wherein said alkaline agent in said subcoating layer comprises an inorganic basic salt.

42. (Previously presented) The method of claim 27, wherein said subcoating layer includes at least one cellulosic polymer selected from the group consisting of hydroxypropyl methylcellulose (HPMC), ethylcellulose and hydroxypropyl cellulose (HPC), or a mixture thereof.

43. (Canceled)

44. (Previously presented) The method of claim 27, wherein said subcoating layer comprises at least one surfactant selected from the group

consisting of polysorbate 80 and sodium lauryl sulfate.

45. (Canceled)

46. (Previously presented) The method of claim 27, wherein said enteric coating material includes at least one enteric material selected from the group consisting of hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylic acid methyl methacrylate and polymethacrylic acid ethyl methacrylate.

47. (Previously presented) The method of claim 27, wherein said enteric coating material further comprises a plasticizer selected from the group consisting of a citric acid ester and a phthalic acid ester.

48. (Canceled)

49. (Original) The method of claim 27, wherein said substrate is an active core for containing lansoprazole.

50. (Original) The method of claim 49, wherein said active core is selected from the group consisting of a pellet, a bead and a tablet.

51. (Withdrawn) A stable composition for lansoprazole, the composition comprising:

(a) a neutral core; and

(b) an active coating containing lansoprazole base, said active coating being layered over said neutral core to form a coated core;

(c) a subcoating layer for coating said coated core, said subcoating layer comprising an alkaline agent; and

(d) an enteric coating material layered over said subcoating layer; wherein said active coating is characterized in that said active coating does not include an alkaline agent and such that the composition is in a form of a pellet.

52. (Withdrawn) The composition of claim 2, wherein said neutral core has a size in a range of from about 80 to about 1000 microns.

53. (Withdrawn) A stable composition for Lansoprazole, the composition comprising:

(a) a substrate, said substrate comprising lansoprazole or a pharmaceutically suitable salt thereof;

(b) a subcoating layer comprising an alkaline agent;

(c) an enteric coating material layered over said subcoating layer to form enteric coated pellets;

wherein said enteric coated pellets are compressed into a tablet dosage form.

54. (Withdrawn) The composition of claim 53, wherein said substrate features:

i) a neutral core; and

ii) an active coating containing lansoprazole, said active coating being layered over said neutral core;

such that the composition is in a form of a pellet.

55. (Withdrawn) The composition of claim 54, wherein said neutral core has a size in a range of from about 80 to about 500 microns.

56. (Withdrawn) The composition of claim 55, wherein said size is in a range of from about 200 to about 300 microns.

57. (Withdrawn) The composition of claim 53, wherein said enteric coating does not include a plasticizer.

58. (Previously presented) A method for administering a therapeutically effective amount of lansoprazole to a subject comprising:

administering orally to the subject a stable composition for lansoprazole comprising:

(a) a substrate, said substrate comprising an active core containing lansoprazole or a pharmaceutically suitable salt thereof as sole pharmaceutically active ingredient and a surfactant, wherein said substrate is characterized in that said substrate does not include an alkaline agent;

(b) a subcoating layer for coating said substrate, said subcoating layer comprising an alkaline agent comprising sodium stearate; and

(c) an enteric coating material layered over said subcoating layer.

59. (Previously presented) A method for administering a therapeutically effective amount of lansoprazole to a subject comprising:

administering orally to the subject a stable composition for lansoprazole comprising:

(a) a substrate, said substrate comprising

i) a neutral core; and

ii) an active coating containing lansoprazole or a pharmaceutically suitable salt thereof as sole pharmaceutically active ingredient and a surfactant, said active coating being layered over said neutral core, wherein said substrate is characterized in that said substrate does not include an alkaline agent;

(b) a subcoating layer for coating said substrate, said subcoating layer comprising an alkaline agent comprising sodium stearate; and

(c) an enteric coating material layered over said subcoating layer.

EVIDENCE APPENDIX

See attached sheets from US Pharmacopeia, previously submitted with the amendment of September 12 2009 which was entered by the Examiner.

RELATED PROCEEDINGS APPENDIX

None

uble in aqueous solutions of mineral acids; slightly soluble in acetone, in chloroform, in alcohol, and in ether.

Levonorgestrel: White or practically white, odorless powder. Practically insoluble in water; soluble in chloroform; slightly soluble in alcohol.

Levorphanol Tartrate: Practically white, odorless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. Melts, in a sealed tube, at about 110°, with decomposition.

Levothyroxine Sodium: Light yellow to buff-colored, odorless, tasteless, hygroscopic powder. Is stable in dry air but may assume a slight pink color upon exposure to light. The pH of a saturated solution is about 8.9. Very slightly soluble in water; soluble in solutions of alkali hydroxides and in hot solutions of alkali carbonates; slightly soluble in alcohol; insoluble in acetone, in chloroform, and in ether.

Lidocaine: White or slightly yellow, crystalline powder. Has a characteristic odor and is stable in air. Practically insoluble in water; very soluble in alcohol and in chloroform; freely soluble in benzene and in ether. Dissolves in oils.

Lidocaine Hydrochloride: White, odorless, crystalline powder, having a slightly bitter taste. Very soluble in water and in alcohol; soluble in chloroform; insoluble in ether.

Lime: Hard, white or grayish-white masses or granules, or white or grayish white powder. Is odorless. Slightly soluble in water; very slightly soluble in boiling water.

Lincomycin Hydrochloride: White or practically white, crystalline powder. Is odorless or has a faint odor. Is stable in the presence of air and light. Its solutions are acid and dextrorotatory. Freely soluble in water; soluble in dimethylformamide; very slightly soluble in acetone.

Lincomycin Hydrochloride Injection: Clear, colorless to slightly yellow solution, having a slight odor.

Lincomycin Hydrochloride Soluble Powder: White to off-white, or light tan free-flowing, fine powder.

Lindane: White, crystalline powder, having a slight, musty odor. Practically insoluble in water; freely soluble in chloroform; soluble in dehydrated alcohol; sparingly soluble in ether; slightly soluble in ethylene glycol.

Linoleoyl Polyoxylglycerides: Amber, oily liquids. May develop deposit after prolonged storage periods at 20°. Freely soluble in methylene chloride; practically insoluble but dispersible in water. *NF category:* Ointment base; solvent.

Liothyronine Sodium: Light tan, odorless, crystalline powder. Very slightly soluble in water; slightly soluble in alcohol; practically insoluble in most other organic solvents.

Lisinopril: White, crystalline powder. Melts at about 160°, with decomposition. Soluble in water; sparingly soluble in methanol; practically insoluble in alcohol, in acetone, in acetonitrile, and in chloroform.

Lithium Carbonate: White, granular, odorless powder. Sparingly soluble in water; very slightly soluble in alcohol. Dissolves, with effervescence, in dilute mineral acids.

Lithium Citrate: White, odorless, deliquescent powder or granules, having a cooling, faintly alkaline taste. Freely soluble in water; slightly soluble in alcohol.

Loperamide Hydrochloride: White to slightly yellow powder. Melts at about 225°, with some decomposition. Freely soluble in methanol and in chloroform; slightly soluble in water and in dilute acids; very slightly soluble in isopropyl alcohol.

Loratadine: White to off-white powder. Freely soluble in acetone, in chloroform, in methanol, and in toluene; insoluble in water.

Lorazepam: White or practically white, practically odorless powder. Insoluble in water; sparingly soluble in alcohol; slightly soluble in chloroform.

Losartan Potassium: White to off-white powder. Freely soluble in water; soluble in isopropyl alcohol; slightly soluble in acetonitrile.

Lovastatin: White to off-white, crystalline powder. Freely soluble in chloroform; soluble in acetone, in acetonitrile, and in methanol; sparingly soluble in alcohol; practically insoluble in hexane; insoluble in water.

Loxapine Succinate: White to yellowish, crystalline powder. Is odorless.

Lutein: Red, crystalline powder. Soluble in ethanol, in ethyl acetate, and in methylene chloride; partially soluble in hexane.

Lysine Acetate: White, odorless crystals or crystalline powder, having an acid taste. Freely soluble in water.

Lysine Hydrochloride: White, odorless powder. Freely soluble in water.

Mafenide Acetate: White to pale yellow, crystalline powder. Freely soluble in water.

Magaldrate: White, odorless, crystalline powder. Insoluble in water and in alcohol; soluble in dilute solutions of mineral acids.

Milk of Magnesia: White, opaque, more or less viscous suspension from which varying proportions of water usually separate on standing. pH is about 10.

Magnesium Aluminometasilicate: White powder or granules having an amorphous structure. Partially soluble in acids and in alkalies; practically insoluble in water and in alcohol.

Magnesium Aluminosilicate: White powder or granules having an amorphous structure. Partially soluble in acids and in alkalies; practically insoluble in water and in alcohol.

Magnesium Aluminum Silicate: Odorless, tasteless, fine (micronized) powder, small cream to tan granules, or small flakes that are creamy when viewed on their flat surfaces and tan to brown when viewed on their edges. Insoluble in water and in alcohol. Swells when added to water or glycerin. *NF category:* Suspending and/or viscosity-increasing agent.

Magnesium Carbonate: Light, white, friable masses or bulky, white powder. Is odorless, and is stable in air. Practically insoluble in water to which, however, it imparts a slightly alkaline reaction; insoluble in alcohol, but is dissolved by dilute acids with effervescence.

Magnesium Chloride: Colorless, odorless, deliquescent flakes or crystals, which lose water when heated to 100° and lose hydrochloric acid when heated to 110°. Very soluble in water; freely soluble in alcohol.

Magnesium Citrate Oral Solution: Colorless to slightly yellow, clear, effervescent liquid, having a sweet, acidulous taste and a lemon flavor.

Magnesium Gluconate: Colorless crystals or white powder or granules. Is odorless and tasteless. Freely soluble in water; very slightly soluble in alcohol; insoluble in ether.

Magnesium Hydroxide: Bulky, white powder. Practically insoluble in water and in alcohol; soluble in dilute acids.

Magnesium Oxide: Very bulky, white powder or relatively dense, white powder or granulated powder. Soluble in dilute acids; practically insoluble in water; insoluble in alcohol.

Magnesium Phosphate: White, odorless, tasteless powder. Almost insoluble in water; readily soluble in diluted mineral acids.

Magnesium Salicylate: White, odorless, efflorescent, crystalline powder. Freely soluble in methanol; soluble in alcohol and in water; slightly soluble in ether.

Magnesium Silicate: Fine, white, odorless, tasteless powder, free from grittiness. Insoluble in water and in alcohol. Is readily decomposed by mineral acids. *NF category:* Glidant and/or anticaking agent.

Magnesium Stearate: Very fine, light, white powder, slippery to touch. Insoluble in water, in alcohol, and in ether. *NF category:* Tablet and/or capsule lubricant.

Magnesium Sulfate: Small, colorless crystals, usually needle-like, with a cooling, saline, bitter taste. It effloresces in warm, dry air. Freely soluble in water; freely (and slowly) soluble in glycerin; very soluble in boiling water; sparingly soluble in alcohol.

Magnesium Trisilicate: Fine, white, odorless, tasteless powder, free from grittiness. Insoluble in water and in alcohol. Is readily decomposed by mineral acids.

Malathion: Clear, colorless, or slightly yellowish liquid, having a characteristic odor. Congeals at about 2.9°. Slightly soluble in

Sodium Caprylate: A white, crystalline powder. Very soluble or freely soluble in water; freely soluble in acetic acid; sparingly soluble in alcohol; practically insoluble in acetone.

Sodium Carbonate: Colorless crystals, or white, crystalline powder or granules. Is stable in air under ordinary conditions. When exposed to dry air above 50°, the hydrous salt effloresces and, at 100°, becomes anhydrous. Freely soluble in water, but still more soluble in boiling water. *NF category:* Alkalizing agent.

Sodium Cetostearyl Sulfate: A white or pale yellow, amorphous or crystalline powder. Soluble in hot water giving an opalescent solution; partly soluble in alcohol; practically insoluble in cold water.

Sodium Chloride: Colorless, cubic crystals or white crystalline powder. Has a saline taste. Freely soluble in water; and slightly more soluble in boiling water; soluble in glycerin; slightly soluble in alcohol. *NF category:* Tonicity agent.

Sodium Chloride Inhalation Solution: Clear, colorless solution.

Bacteriostatic Sodium Chloride Injection: Clear, colorless solution, odorless or having the odor of the bacteriostatic substance. *NF category:* Vehicle (sterile).

Sodium Chloride Irrigation: Clear, colorless solution.

Sodium Citrate: Colorless crystals, or white, crystalline powder. Hydrous form freely soluble in water and very soluble in boiling water. Insoluble in alcohol. *NF category:* Buffering agent.

Sodium Citrate and Citric Acid Oral Solution: Clear solution having the color of any added preservative or flavoring agents.

Sodium Dehydroacetate: White or practically white, odorless powder, having a slight characteristic taste. Freely soluble in water, in propylene glycol, and in glycerin. *NF category:* Antimicrobial preservative.

Sodium Fluoride: White, odorless powder. Soluble in water; insoluble in alcohol.

Sodium Formaldehyde Sulfoxylate: White crystals or hard, white masses, having the characteristic odor of garlic. Freely soluble in water; slightly soluble in alcohol, in ether, in chloroform, and in benzene. *NF category:* Antioxidant.

Sodium Hydroxide: White, or practically white, fused masses, in small pellets, in flakes, or sticks, and in other forms. Is hard and brittle and shows a crystalline fracture. Exposed to the air, it rapidly absorbs carbon dioxide and moisture. Freely soluble in water and in alcohol. *NF category:* Alkalizing agent.

Sodium Hypochlorite Solution: Clear, pale greenish-yellow liquid, having the odor of chlorine. Is affected by light.

Sodium Iodide: Colorless, odorless crystals, or white, crystalline powder. Is deliquescent in moist air, and develops a brown tint upon decomposition. Very soluble in water; freely soluble in alcohol and in glycerin.

Sodium Lactate Solution: Clear, colorless or practically colorless, slightly viscous liquid, odorless or having a slight, not unpleasant odor. Miscible with water. *NF category:* Buffering agent.

Sodium Lauryl Sulfate: Small, white or light yellow crystals having a slight, characteristic odor. Freely soluble in water, forming an opalescent solution. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sodium Metabisulfite: White crystals or white to yellowish, crystalline powder, having the odor of sulfur dioxide. Freely soluble in water and in glycerin; slightly soluble in alcohol. *NF category:* Antioxidant.

Sodium Monofluorophosphate: White to slightly gray, odorless powder. Freely soluble in water.

Sodium Nitrite: White to slightly yellow, granular powder, or white or practically white, opaque, fused masses or sticks. Has a mild, saline taste and is deliquescent in air. Its solutions are alkaline to litmus. Freely soluble in water; sparingly soluble in alcohol.

Sodium Nitrite Injection: Clear, colorless liquid.

Sodium Nitroprusside: Reddish-brown, practically odorless, crystals or powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; insoluble in benzene.

Dibasic Sodium Phosphate (*dried*)**:** White powder that readily absorbs moisture. Freely soluble in water; insoluble in alcohol. *NF category:* Buffering agent.

Dibasic Sodium Phosphate (*heptahydrate*)**:** Colorless or white, granular or caked salt. Effloresces in warm, dry air. Its solutions are alkaline to phenolphthalein TS, a 0.1 M solution having a pH of about 9. Freely soluble in water; very slightly soluble in alcohol. *NF category:* Buffering agent.

Monobasic Sodium Phosphate: Colorless crystals or white, crystalline powder. Is odorless and is slightly deliquescent. Its solutions are acid to litmus and effervesce with sodium carbonate. Freely soluble in water; practically insoluble in alcohol. *NF category:* Buffering agent.

Tribasic Sodium Phosphate: The formula for a crystalline material is approximately $4(Na_3PO_4 \cdot 12H_2O)NaOH$. It occurs as white, odorless crystals or granules or as a crystalline powder. It is freely soluble in water; insoluble in alcohol. The pH of a 1 in 100 solution is between 11.5 and 12.0.

Sodium Polystyrene Sulfonate: Golden brown, fine powder. Is odorless and has a characteristic taste. Insoluble in water.

Sodium Propionate: Colorless, transparent crystals or granular, crystalline powder. Is odorless, or has a faint acetic-butyric odor and is deliquescent in moist air. Very soluble in water; soluble in alcohol. *NF category:* Antimicrobial preservative.

Sodium Salicylate: Amorphous or microcrystalline powder or scales. Is colorless, or has not more than a faint, pink tinge. Is odorless, or has a faint, characteristic odor, and is affected by light. A freshly made solution (1 in 10) is neutral or acid to litmus. Freely (and slowly) soluble in water and in glycerin; very soluble in boiling water and in boiling alcohol; slowly soluble in alcohol.

Sodium Starch Glycolate: White, tasteless, odorless, relatively free-flowing powder; available in several different viscosity grades. A 2% (w/v) dispersion in cold water settles, on standing, in the form of a highly hydrated layer. *NF category:* Tablet disintegrant.

Sodium Stearate: Fine, white powder, soapy to the touch, usually having a slight, tallow-like odor. Is affected by light. Its solutions are alkaline to phenolphthalein TS. Slowly soluble in cold water and in cold alcohol; readily soluble in hot water and in hot alcohol. *NF category:* Emulsifying and/or solubilizing agent.

Sodium Stearyl Fumarate: Fine, white powder. Slightly soluble in methanol; practically insoluble in water. *NF category:* Tablet and/or capsule lubricant.

Sodium Sulfate: Large, colorless, odorless, transparent crystals, or a granular powder. Effloresces rapidly in air, liquefies in its water of hydration at about 33°, and loses all of its water of hydration at about 100°. Freely soluble in water; soluble in glycerin; insoluble in alcohol.

Sodium Sulfite: Colorless crystals. Freely soluble in water; very slightly soluble in alcohol. *NF category:* Antioxidant.

Sodium Tartrate: Transparent, colorless, odorless crystals. Freely soluble in water; insoluble in alcohol. *NF category:* Sequestering agent.

Sodium Thiosulfate: Large, colorless crystals or coarse, crystalline powder. Is deliquescent in moist air and effloresces in dry air at temperatures exceeding 33°. Its solutions are neutral or faintly alkaline to litmus. Very soluble in water; insoluble in alcohol. *NF category:* Antioxidant.

Sorbic Acid: Free-flowing, white, crystalline powder, having a characteristic odor. Slightly soluble in water; soluble in alcohol and in ether. *NF category:* Antimicrobial preservative.

Sorbitan Monolaurate: Yellow to amber-colored, oily liquid, having a bland, characteristic odor. Soluble in mineral oil; slightly soluble in cottonseed oil and in ethyl acetate; insoluble in water. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

Sorbitan Monooleate: Viscous, yellow to amber-colored, oily liquid, having a bland, characteristic odor. Insoluble in water and in propylene glycol. Miscible with mineral and vegetable oils. *NF category:* Emulsifying and/or solubilizing agent; tablet and/or capsule lubricant; wetting and/or solubilizing agent.

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